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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,928	05/05/2006	Yechezkel Barenholz	BARENHOLZ13	4078

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
05/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,928	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	EMILY M. LE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/01/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-116 and 118-127* is/are pending in the application.

4a) Of the above claim(s) *76-107* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-116 and 118-127* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

1. Applicant's reminder of the Office's rejoinder practice has been noted. Rejoinder will be considered upon the allowance of the product.

Status of Claims

2. Claims 1-75, 117 and 128-134 are cancelled. Claims 76-116 and 118-127 are pending. Claims 76-107 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/30/2009. Claims 108-116 and 118-127 are under examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 108-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jorgensen et al.[1]

In response to the rejection, Applicant amended the claims to include the recitations "an amount of", "an immune response modulating", and "and the amount of said sphingoid polyalkylamine conjugate being effective to enhance the activity of said biologically active molecule on the immune response of the subject". Applicant argues

that Jorgensen et al. fails to teach or suggest that a sphingoid polyalkylamine conjugate will enhance the activity of an immune response modulating biologically active molecule on the immune system nor its superiority. Applicant also criticizes the Office for noting that DNA, mRNA, antisense oligonucleotides, proteins and drugs are biologically active molecules that modulates and induces the immune response. Specifically, Applicant argues that Jorgensen et al. discloses that sphingoid polyalkylamine conjugate is useful in gene therapy, and gene therapy does not necessarily involve the immune system. Applicant further submits that not every protein or drug has the capability to modulate the immune response. Applicant additionally submits that the claimed invention is a vaccine, a preparation that improves immunity to a particular disease, which Jorgensen et al. does not teach.

Applicant also argues unexpected properties. That is, Applicant argues that the claimed invention surprisingly act as an adjuvant. And, Applicant notes that Jorgensen et al. does not teach that sphingoid polyalkylamine conjugate has adjuvant properties.

Directing at claim 110, Applicant argues that there is absolutely no motivation to use an adjuvant in gene therapy as it is only obvious to use an adjuvant with a vaccine.

Applicant's arguments have been considered, however, it is not found persuasive. The recitation "vaccine" is interpreted as a composition with an intended use. The intended use of the claimed composition as a vaccine must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is

[1] Jorgensen et al. U.S. PreGrant Pub. No. 2002/0188023 A1, published December 12, 2002.

capable of performing the intended use, then it meets the claim. In the instant case, the cited recitation do not result in a structural difference between the claimed invention and the prior art, and the prior art structure is capable of performing the intended use. Furthermore, Jorgensen et al. suggests the use of sphingoid-polyalkylamine conjugate in therapy as a vaccine. [Paragraphs 0003 and 0014, in particular.] Directing at claim 110, thus, the position taken by the Office with regard to the cited claim is proper. Jorgensen et al. suggests the use of sphingoid polyalkylamine conjugate with a biologically active molecule to act as vaccines. And it is obvious, as stated on the record by Applicant, to include adjuvants in vaccines.

Additionally, MPEP 2112 [I] provides:[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). In the instant case, while Applicant's discovery of the unexpected adjuvant property of sphingoid polyalkylamine conjugate is appreciated, however, such discovery does not render the claimed invention patentable because Jorgensen et al. teaches sphingoid polyalkylamine conjugate. The sphingoid polyalkylamine conjugate of Jorgensen et al. is the same as the sphingoid polyalkylamine conjugate recited in the claims. The discovered adjuvant property is inherent of sphingoid polyalkylamine conjugate.

Regarding Applicant's criticism of the Office for noting that DNA, mRNA, antisense oligonucleotides, proteins and drugs are biologically active molecules that

modulates and induces the immune response, it should be noted that Jorgensen et al. teaches the use of gene therapy to attain a desired therapeutic function. [Paragraphs 0002-0003, in particular.] Jorgensen et al. also teaches that examples of therapy include treating cancer, treat cystic fibrosis, treat neurodegenerative and cardiovascular disorders, treat rheumatoid arthritis, treat AIDS (HIV) infection and treat CMV infection. These therapies require an immune response. In the event that Applicant continues with this argument, it should be noted that Jorgensen et al. also the insertion of antigens and cytokines to act as vaccines as an example of therapy.

In the instant case, Jorgensen et al. teaches the use of sphingoid polyalkylamine conjugate as a delivery vehicle for drug and genes for therapeutic functions. [Paragraphs 0014 and 0033, in particular.] The teachings of Jorgensen et al. are not merely limited to the use of sphingoid polyalkylamine conjugate in gene therapies.

The claims are directed toward a composition comprising a sphingoid-polyalkylamine conjugate and a biologically active molecule. Claim 109, which depends on claim 108, requires that the biologically active molecule be effective to stimulate or enhance the immune response of said subject. Claim 110, which depends on claim 109, requires that the composition to further comprise an immunostimulating agent. Claim 111, which depends on claim 108, requires that the conjugate comprise a sphingoid backbone carrying, vial a carbamoyl bond and at least one polyalkylamine chain. Claim 112, which depends on claim 111, requires the sphingoid backbone be selected from the group consisting of ceramide, dihydroceramide, phytoceramide, dihydrophytoceramide, ceramine, dihydrocramine, phytoceramine, and

dihydrophytoceramine. Claim 113, which depends on claim 112, limits the sphingoid to ceramide. Claim 114, which depends on claim 108, requires that the polyalkylamine chain be spermine, spermidine or polyalkylamine analog of spermine or spermidine.

Jorgensen et al. teaches a composition comprising a lipid-polyalkylamine conjugate. [Entire reference, in particular.] The lipid that Jorgensen et al. teaches is ceramide. [Paragraph 064, in particular.] The polyalkylamine that Jorgensen et al. teaches includes spermine and spermidine. [Paragraph 0053, in particular.] Jorgensen et al. also teaches that the lipid-polyalkylamine conjugate can be linked using a hydrocarbyl group, including carbamoyl. [Paragraphs 0047 and 0066, in particular.] In the instant case, Jorgensen et al. teaches the claimed sphingoid-polyalkylamine conjugate.

Jorgensen et al. did not include a biologically active molecule with the composition. However, Jorgensen et al. teaches that the compound is a cationic liposome that can be used to facilitate delivery of therapeutic agents such as DNA, mRNA, antisense oligonucleotides, proteins and drugs into cells—all of which are biologically active molecules that modulates and induces the immune response. [Page 1, in particular.] Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to include a biologically active molecule with the lipid-polyalkylamine conjugate of Jorgensen et al. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to facilitate delivery of molecules. One of ordinary skill in the art would have had a reasonable

expectation of success for doing so because Jorgensen et al. discloses that lipid-polyalkylamine conjugates are effective to facilitate delivery of drugs into cells.

Additionally, it would have been prima facie obvious for one of ordinary skill in the art to also include an immunostimulating agent, such as an adjuvant to the composition rendered obvious by Jorgensen et al. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to stimulate the immune response induced by the composition rendered obvious by Jorgensen et al. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvants with therapeutic agents such as biologically active molecules is routinely practiced in the art.

5. Claims 108-116 and 118-127 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al.,[2] in view of Jorgensen et al.[3]

In response to the rejection, Applicant refers to the argument and criticism noted for Jorgensen et al. Applicant also argues that Miller et al. fails to add to the deficiencies noted of Jorgensen et al. Applicant also argues that claim 116 should be considered on its own right. Applicant argues that there would be no known reason to deliver a molecule derived from influenza virus into a cell. Therefore, Applicant concludes that it would not be obvious to use this molecule as the biologically active molecule of Jorgensen or Miller. Applicant argues that the claim is to a flu vaccine, and claim 116 has unexpected results as a sphingoid polyalkylamine conjugate act as an adjuvant.

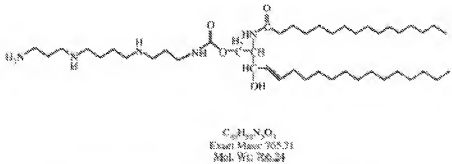
[2] Miller et al. WO 97/45442, published December 4, 1997.
[3] Jorgensen et al. U.S. PreGrant Pub. No. 2002/0188023 A1, published December 12, 2002.

Applicant's arguments have been considered, however, it is not found persuasive. Arguments presented against Jorgensen et al. is provided in the above paragraph, paragraph no. 4. Regarding claim 116, it should be noted that the claim is considered on its own right. Every claim is considered on its own right. With regard to Applicant's argument that "there would be no known reason to deliver a molecule derived from influenza virus into a cell", an obvious reason is to induce an immune response. As noted above, Jorgensen et al. teaches the use of sphingoid polyalkylamine conjugate as a delivery vehicle for drugs and gene. Thus, in the instant case, as stated in the rejection, it would have been prima facie obvious for one of ordinary skill in the art to include a biologically active molecule, including those derived from the influenza virus with the lipid-polyalkylamine conjugate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to facilitate delivery of molecules, including those derived from the influenza virus to stimulate an immune response. Applicant is further reminded that arguments cannot take place of evidence. Arguments should be substantiated with supporting evidence.

The significance of claims 108-114 are provided above. Claim 115, which depends on claim 108, requires that the sphingoid-polyalkylamine conjugate be N-palmitoyl D-erythoro sphingosyl carbamoyl-spermine (CCS). Claim 116, which depends on claim 115, requires the biologically active molecule be derived from influenza virus or is an analog of a molecule derived from influenza virus. Claim 118, which is interpreted as depending on claim 108, specifies the broad structure for the sphingoid-polyalkylamine conjugate. Claims 119-127, which depends on claim 118, are directed

to defining the various variables set forth in the structure provided in claim 118, wherein CCS encompasses the defined variables set forth therein.

CCS has the following structure:



$C_{39}H_{79}N_5O_3$
Exact Mass: 665.71
Mol. Wt.: 666.24

Fig. 1. *N*-palmitoyl D-erythro-sphingosyl-1-O-carbamoyl-spermine, CCS.

Miller et al. teaches a composition comprising a lipid-polyalkylamine conjugate. [Entire reference, in particular.] [Figure 5, in particular.] The lipid that Miller et al. teaches is cholesterol. The polyalkylamine that Miller et al. teaches includes spermine and spermidine and its analogs. [Figure 4, in particular.] Miller et al. also teaches the use of carbamoyl group to link the lipid-polyalkylamine conjugate. [Figure 5, in particular.] In the instant case, Miller et al. teaches a composition comprising cholesterol carbamoyl spermine and its analogs.

Miller et al. did not teach the use of ceramide as the lipid. However, at the time the invention was made, Jorgensen et al. teaches the use of ceramide as an alternative lipid to cholesterol. [Paragraph 0064, in particular.] Jorgensen et al. establishes that cholesterol and ceramide can be used in place of each other, art recognized equivalents. Therefore, it would have been prima facie obvious for one of ordinary skill

in the art to use ceramide as the lipid in the lipid-polyalkylamine conjugate of Miller et al. In the instant case, both Miller et al. and Jorgensen et al. teach that lipid-polyalkylamine compound is a cationic liposome that can be used to facilitate delivery of therapeutic agents such as DNA, mRNA, antisense oligonucleotides, proteins and drugs into cells—all of which are biologically active molecules that modulates and induces the immune response. Additionally, the use of ceramide in place of cholesterol renders the compound of Miller et al. as ceramide carbamoyl-spermine (CCS). One of ordinary skill in the art would have been motivated to do to make a composition that facilitates delivery of therapeutic agents. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the use of one lipid for another, art recognized equivalents, is routinely practiced in the art.

Neither Miller et al. nor Jorgensen et al. not include a biologically active molecule with the composition. However, as noted above, both teach that the compound is a cationic liposome that can be used to facilitate delivery of therapeutic agents such as DNA, mRNA, antisense oligonucleotides, proteins and drugs into cells—all of which are biologically active molecules that modulates and induces the immune response. Thus, at the time the invention was made, it would have been prima facie obvious for one of ordinary skill in the art to include a biologically active molecule, including those derived from the influenza virus with the lipid-polyalkylamine conjugate. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to facilitate delivery of molecules, including those derived from the influenza virus to

stimulate an immune response. One of ordinary skill in the art would have had a reasonable expectation of success for doing so because both references disclose that lipid-polyalkylamine conjugates are effective to facilitate delivery of drugs into cells.

Additionally, it would have been prima facie obvious for one of ordinary skill in the art to also include an immunostimulating agent, such as an adjuvant to the composition rendered obvious by Miller et al. and Jorgensen et al. One of ordinary skill in the art, at the time the invention was made would have been motivated to do so to stimulate the immune response induced by the composition rendered obvious by Jorgensen et al. One of ordinary skill in the art, at the time the invention was made would have had a reasonable expectation of success for doing so because the use of adjuvants with therapeutic agents such as biologically active molecules is routinely practiced in the art.

Conclusion

6. No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to EMILY M. LE whose telephone number is (571)272-0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/EMILY M LE/
Primary Examiner, Art Unit 1648

/E. M. L./
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